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54 Metal oxide composite with regulated release of active ingredients.

57 The invention concerns composites of a metal oxide matrix and at least and one incorporated homogeneous, molecularly disperse and non crystalline component. A process for its manufacture as well as applications for the composites.
The incorporated component can include an active ingredient and possibly one or more control materials.
As active ingredients one can use liquid or solid substances of plant or organic origin, which interact biologically with living organism.
The active ingredients are introduced into the silicon dioxide matrix by sol-gel technology.
As control materials one can use low-molecular water-soluble materials, polyionic compounds, micro-porous fillers as well as high-boiling solvents.
The release of organic liquids or oils from the matrix can be controlled either by penetrating compounds or by controlled temperature increase.
The composites according to the invention find use in the production of pharmaceuticals, cosmetics, body care products, bacteriostatics or bacteriocidins, insecticides and pesticides.

The invention concerns composites consisting of metal oxide and at least one component included there-in

The invention especially concerns composites for controlled release of active components. which contains a silicon dioxide matrix. where the SiO_2. can be partly replaced by Al_2O_3 or MgO. at least one incorporated active ingredient and possibly one or more control materials. a process for their manufacture as well as their use for specific medicinal preparations.

The invention concerns further specific powders and films of metal oxides. which have at least one incorporated organic liquid or oil. processes for their manufacture. as well as their use for medicinal preparations. cosmetics. body care products. bacteriostatics or bacteriocidins. insecticides and pesticides.

The invention can especially be applied where slow release of a liquid or an oil to the surroundings is desired. or where protection from evaporation or interaction with the surrounding media is needed.

It is known. to improve the mechanical and chemical stability as well as to control the release of medicinal active materials by mixing or coating them with aid materials. In general one uses mixtures of different organic aid materials such as e. g. carbon hydrate derivatives and / or gel forming high-polymeric materials such as gelatin or cellulose- derivatives. Their disadvantage is, especially for depositories . that the active ingredient release is strongly dependent upon the environment, and as such it becomes difficult to control the release in the stomach - digestive tract. resulting in problematic dosage control.

Further problems arrive for the use of organic aid materials due to different tolerance levels for users. as well as due to the fact, that optimal effects can only be achieved by mixtures of compounds. requiring difficult development processes and application testing.

To avoid the above mentioned drawbacks. there have recently been efforts to use inorganic materials as aid matrixes. Among the materials evaluated, silicon dioxide has a special position; it is cheap, easily available. non toxic and stable to body fluids. But a series of difficulties are encountered, when silicon dioxide has to be loaded with active ingredients.

One is starting with solid silicon dioxide particles and lets the active ingredients adsorb to the surface of the silicon dioxide particles. e. g. by using finely divided SiO_2 powders (JP 04159222A), colloidal SiO_2 (EP 487335-A1), micro-porous silica gel (EP 336014 A) or porous glass particles (GB 2146531 A), or by use of stabilized SiO_2 -dispersions, stabilized through polymeric acids (EP 294206 A), stabilized through positively charged dispersants or cat-ionic polymers (EP 478326 A). For all these processes there are problems of reproducible loading with the active ingredients due to variations in particle surfaces. Further there is limited possibility for manufacture with high active ingredient / SiO_2 -proportions and little possibility to influence the rate of active ingredient release.

The sol-gel technology gives new possibilities for incorporation of organic materials into a metal oxide matrix. Here EP 0439318 A2 describes a technology where metal alkoxides are hydrolyzed and polycondensed in the presence of an organic material to obtain doped glasses for chemical exchange reactions. This process leads when

used with bio-active ingredients to extensive loss in activity. since the active ingredients are locked into the SiO_2 - matrix; e.g. glucose oxidase loaded xero-gel-sensors for determination of glucose lead to unacceptable reaction times of 12 min. (S. Braun et. al. J. Non-Cryst. Solids 147 / 48 (1992) 739).
The first possibility for improving the reactivity of enzyme loaded sol - gel - layers by using penetration aids was described in the German patent application P 4308146.0 (03.13.93). While the named application describes possibilities to improve the reactivity from the layer, it is necessary, when different types of pharmaceutical agents are to be encapsulated in metal oxides. to modify the diffusion characteristics of the active ingredient. Such possibilities have not been known until now.
It is further known. that numerous organic liquids or high vapor pressure solids are transferred to solid form to insure application and avoid evaporation when used as pharmaceutics. pesticides. bacteriocidins. explosives. dusting compounds etc.
For economic and ecologic reasons, one here aims at using inorganic carriers, especially metal oxides. Here one most often utilizes adsorption of liquids at porous surfaces. But this method has some drawbacks. as described e. g. in EP 143221, resulting in slow evaporation of the liquids from open systems. because they are only held physically at the solid surface. A further disadvantage is, that the adsorbed materials are unprotected against attack by the atmosphere and then can become oxidized or hydrolyzed.
For this reason. there have been intensive efforts to search for encapsulations, which inhibit the undesirable evaporation and insure long-term stability. For this purpose, it has been proposed for non water containing liquids adsorbed on a metal oxide powder to additionally encapsulate with a film forming polymer such as gelatin (NL 7214978 , US 630928). Such multi-step methods are complicated technologically. and do only permit limited controlled release of the liquid, since a uniform encapsulation of the metal oxide particles containing the liquid is difficult. and because desorption processes due to interaction with the polymer as well as the solvent can take place during the subsequent encapsulation process.
At this time, no universal method is available for encapsulation of liquids in metal oxides. which is technically simple and reproducible. assures long-term stability of the incorporated liquids and makes possible a controlled release from the matrix.
The task then was to develop a new. improved possibility for incorporation of active ingredients into a metal oxide matrix, which could be realized with simple and few means of support. and then further to list applications for the composites.
This task was solved by the composites with the characteristics as listed in claim 1. and with the additional features listed in claims 16. 19 and 20. as well as by the applications listed in claims 21 and 22. Advantageous practical forms of the invention can be derived from the sub-claims.
A special task was to find new possibilities for addition of active ingredients into a silicon dioxide matrix. which could be realized with simple and few means and which made possible a controlled release of the active ingredient from the matrix.
Surprisingly , this task was solved with simple means, according to this invention, by incorporating the active ingredients in a new way in the presence of one or several control materials into a modified silicon dioxide matrix. whereby active ingredient

silicon dioxide composites with controlled release are obtained.
A further task was also to develop new possibilities for incorporation of liquids and oils into metal oxide matrixes. which could be processed simply and with few additional aids. to assure a high stability of the incorporated liquids and oils. and if desired make possible a controlled release of the liquids and oils from the metal oxide matrix.
Surprisingly , this aspect could be solved simply according to the invention by incorporation of the organic liquids and oils into a metal oxide matrix using sol-gel processing.
It was unexpectedly found. that it is possible to incorporate organic liquids and oils to a large weight proportion into the metal oxide matrix, and to create stable non sticking products (powders. film layers) containing the organic liquids and oils in encapsulated form.
In the following the invention is explained by practical examples.

Example 1

Objectives of the invention according to one practical example are composites for controlled release consisting of a silicon dioxide matrix, where the SiO_2 can partly be replaced by Al_2O_3 or MgO, and containing at least one incorporated active ingredient and possibly one or more control materials.
The production of the composites can be recognized by the feature. that the active ingredient, possibly in the presence of one control material is dissolved or dispersed in a water-organic SiO_2-sol , and directly, or after gel- formation by to removal of solvent, is transferred to an active ingredient composite. Hereby the active ingredient is homogeneously . and for dissolved active ingredients. is incorporated in non-crystalline or generally molecularly disperse form into the SiO_2- matrix. The selection of the synthesis conditions (e. g. the SiO_2/ active ingredient proportion) and the addition of suitable control materials does have a definitive influence upon the swelling and diffusion characteristics of the SiO_2- matrix and result in a controlled release of the active ingredient.
The composite preparations produced have a series of advantages. They are simple to produce and have a controlled release of the active ingredient. No complicated equipment or technology is needed. The technology can be used for a large number of active ingredients, since there is practically no solubility restriction.
The composite synthesis does progress in neutral solutions at moderate temperatures (under 50°C), which makes it possible, to also use active ingredients which are very sensitive to hydrolysis or temperature. One can produce composites with active ingredient proportions ad will.
The composite preparation contains. with the exception of non toxic control materials. no other additives. which results in an excellent compatibility. The active ingredient liberation is adjustable within large ranges by the technology and by the addition of control materials, and one can achieve a large variety of release properties. The resulting preparations can without problem be further processed into medicine. in so-far that they are not already medicine.
The invention composites can. depending upon the desired release properties. be

modified in many ways.
As starting material one uses silicon dioxide- sol in a water-organic solvent which is prepared as known (see C.J. Brinker. G. W. Scherer. Sol-Gel Science. Academic Press Inc. San Diego 1990) through acid or basic catalytic hydrolysis of a tetraalkoxy silane: the organic residual R can nearly be selected at will.

$$Si(OR)_4 + 2\,H_2O \xrightarrow{(Kat)} (SiO_2)_{n,Sol} + 4\,ROH \quad (1)$$

Certain economic advantages are associated with hydrolysis of commercial partly hydrolyzed tetraalkoxy silane (polyalkoxy silane). The hydrolysis catalyzed by acids or bases is preferred carried out at room temperature in organic solvents mixed with water and can be varied dependent upon the solubility of the active ingredient. E. g. it is desirable for water insoluble active ingredients to use a SiO2- sol with no or little water content based upon aprotic solvents such as acetone, dioxane, dimethyl formamide or high boiling alcohols such as methoxypropanol, ethylglycol, so that the water is removed before or simultaneous with the solvent. This new type of processing (reduced water sol, high boiling organic solvent) is the an essential precondition for incorporating water-insoluble active ingredients into the SiO2- matrix in a non-crystalline phase.
For instance,when carbamacepine / SiO2 composites were synthesized using a SiO2 - sols in ethylglycol - water. the dried material was analyzed by x-ray diffraction, and showed only the increased background typically for amorphous compounds; while composites synthesized using a SiO2 - sols in ethanol - water showed clear interference patterns for carbamacepine crystallites. But it is possible, to use g a SiO2 - sols in ethanol - water for encapsulation of water insoluble active ingredients, if one adds higher boiling materials (BP above 100°C), or dries the active ingredient containing SiO2 - sol so fast (e. g. by spray- drying), that one avoids the fractionating during solvent removal. Carbamacepine- SiO2 - sols in ethanol - water which are spray- dried. resulted in composites consisting of about 20 µm large spherical particles, the x-ray diffraction of which again showing only the increased background typically for an amorphous compound.
The SiO2 - content in the sol is generally in the 1 - 30 w % region and is primarily determined by economical factors.
Also the synthesis of mixed metal oxides, e. g. SiO2 / Al2O3 or SiO2 / MgO is easily accomplished. if one before hydrolysis adds the corresponding metal alcoholate in the desired molar proportion to the tetraalkoxy silane.
The hydrolysis can be catalyzed by diluted mineral acids. e. g. 0.01 molar acetic acid. organic acids such as pure of diluted acetic acid, or by basic materials such as aqueous or vapor ammonia, e. g. diluted sodium hydroxide or sodium carbonate solution. In a few special cases the hydrolysis can be carried out using hydrochlorides of weakly basic compounds.

The introduction of active ingredients into the SiO_2 - matrix is accomplished by mixing of the dissolved active ingredient with the SiO_2 - sol or by dissolving the solid ingredient in the sol. For slightly soluble active ingredients one can also use dispersion using a homogenizer. The weight proportion of active ingredient · SiO_2 is generally between 0.05 :1 to 1 : 1; for some active ingredients these proportion limits can be easily increased or decreased.
The invention composites can be treated differently, depending upon the release properties desired. Here there are three essential variables to be taken into account:

(a) The active ingredient / SiO_2 - proportion

As expected the release rate decreases with deceasing active ingredient / SiO_2 - proportion (see Fig 1)

(b) Condensation conditions

There is a possibility to condense the active ingredient / SiO_2 -sol to a gel by changing the pH or by heating:

$$(SiO_2)_{n,Sol} + W \dashrightarrow (SiO_2)_{m,Gel}\text{-}W \quad m > n \qquad (2)$$

In the case of changing the pH. one neutralizes the basic or acid stabilized SiO_2-sol (pH =7) to solidify to the gel. The gel contains the active ingredient in homogeneous distribution. By removal of the solvent from the gel by standard drying processes one obtains a powder active ingredient / SiO_2 - composite (gel -variant). In another process the solvents of the weakly basic or acid sol solution with the active ingredient is directly removed by distillation or spray-drying. (sol-variant). Both variants can be successfully used for incorporation of the active ingredient into the SiO_2 - matrix.
In the cases evaluated by us, the variant gel-formation / drying always led to a more active ingredient encapsulation and to a slower release. than was obtained by the direct drying of the sol (see fig 3). But for both variants the release was additionally controlled by the conditions of drying in a reproducible manner. Generally it was observed, that an increase of drying temperature or a later heat treatment of the active ingredient / SiO_2 - composites slowed the active ingredient release.

(c) Addition of control materials

An especially effective control of the release properties is accomplished by addition of control materials to the active ingredient / SiO_2 - solution at weight proportions from 1 to 50 % in relation to the SiO_2. Surprisingly it was found, that the release properties from the solid SiO_2 - matrix can be modified by addition of materials which change the permeability of the matrix by dissolving out, swelling it, or by inhibiting diffusion .

It was found, that 4 types of control materials are useful:

(1) Low molecular water soluble materials such as sacharide -derivatives, e. g. glucose, lactose, sorbitol, manitol or sacharose, salts or amids of organic acids, e. g. salts of benzoic acid or sorbic acid, amides such as o-benzoic acid sulfimide (Sacharin), acetamide or ureic acid as well as ammonium sulfate or tetraalkyl- ammonium chloride.
These control materials increase the release from the matrix . since they are partly dissolved out of the matrix and increase its permeability.

(2) Polyanionic materials such as salts of polystyrene-sulfonic acid, polyacrylic acid, carboxymethyl cellulose, dextran sulfate, or polycationic compounds such as polydimethyldiallyl -ammonium chloride (PDMDAAC).
These control materials can increase the release of the active ingredients from the matrix by increasing the swelling characteristics. But in specific cases, it is also possible to decrease the release rate, if the active ingredients interact and are bound e. g. .by forming salts in the matrix (e. g. polyacrylic acid / trimipramine - base, fig 6).

(3) Microporous fillers aid the release by increasing the permeability of the matrix ("wicking action ").

(4) High boiling solvents such as phthalic acid ester, glycerin ether or paraffin oil into which the active ingredient is soluble.
It was surprisingly found, that one also can incorporate into the matrix high boiling liquids and oils as control materials. The resulting active ingredient granulates are non sticking, dry and free flowing . By introduction of high boiling liquids it is possible to greatly decrease or increase release of the active ingredient, depending upon the solubility characteristics of the active ingredient in the liquid and the surrounding media.
As an example the oil soluble vitamin K3 (example 1.6, fig. 7) can be introduced into the metal oxide matrix under addition of dibutyl phthalate (DBP) or paraffin oil AB (Paraf). In the release media consisting of 50 % n-propanol, DBP is partly soluble, resulting in a strong increase of release rate. since DBP acts like a transport agent for the release from the matrix. Paraffin oils on the other hand, are nearly insoluble in aqueous alcohols, resulting in a strong decrease of the release rate. since there is little tendency for the oil soluble active ingredient to diffuse into the aqueous alcohol phase .
As can be seen from the examples (see fig. 2 and 4), the release rate of the active ingredient can be strongly accelerated or decelerated depending upon type and concentration of the added control material.
Varying the type an d concentration of the control material it is possibly with a few orienting experiments, for a specific active ingredient to find a composite formulation which under the desired process conditions assures the desired release properties.
An advantage here is the continuous release of active ingredient over a long time span.

The active ingredient composites synthesized according to the invention can be used in many different ways. Especially advantageous is the use for pharmacological preparations with controlled release of active ingredient.. Here one can use the composites directly as powders, granulates or pills as well as in encapsulated, coated or covered shapes. As the examples show. there seem to be no limits with the respect to active ingredient, e. g. one can use neutral, acid or basic, water soluble or water insoluble ingredients. such as alprozolam, carbamacin, clonidin, detajmiumbitrate, diclofenac, diazepam, gilbenclamide, nifedipine, pentoifyline, prazosine, talinilol, verapamil.

The process also makes it possible to encapsulate liquid high boiling active ingredients. This e. g. gives the advantage, instead of hydrochlorides, to encapsulate liquid or low melting active bases (e. g. liquid clomipramine - base or low melting trimipromine - base) into the SiO_2 - matrix, or to modify the release by addition of high boiling control materials, such as phthalic acid ester, glycerin ether or paraffin oil. Similarly it is possible, to introduce fat- soluble or oily vitamins such as vitamin K_3, vitamin A or vitamin E or their mixtures into the SiO_2 - matrix.

Similar to the pharmaceutical active ingredients one can also incorporate active ingredients as used for cosmetics, pesticides and plant protection, if controlled release of the active ingredient is desired.

From the magnitude of process variations, the following examples are given.

Example 1.1 :

(a) General synthesis of pure SiO_2 - sol (Sol A)

50 ml tetraethoxy silane, 200 ml ethanol (ethyl glycol or dioxane) and 100 ml 0,01 N HCl were agitated for 20 h. at room temperature.

(To accommodate the solubility of the active ingredient, the type and concentrations of the organic solvent can be greatly varied . Further one can use commercial partly hydrolyzed products (e. g, polysilisic acid Dynasil 40, Dynasil 220 / Hüls AG) instead of tetraethoxy silane).

(b) Synthesis of SiO_2 - Al_2O_3- sol (Sol B)

10 g tetraethoxy silane and 2 g aluminum triisopropylate are dissolved in 50 ml ethylene glycol monomethyl ester and under agitation is dripped in 5 ml 5 % aqueous ammonium hydroxide solution. After twelve hours, the clear liquid is processed for incorporation of the active ingredient.

(c) Synthesis of SiO_2 - MgO- sol (Sol C)

12.7 g tetraethoxy silane and 0.7 g magnesium methylate are dissolved in 120 ml ethanol. Under agitation is dripped in 5 ml 5 % aqueous ammonium hydroxide solution. After twelve hours a white precipitate is filtered off, and the filtrate is processed for incorporation of the active ingredient.

Example 1.2 :

Carbamacepine - SiO_2 - composites

1 g of the active ingredient Carbamacepin was under heating dissolved in the corresponding amount of sol and gelled by addition of a few drops of 10 % sodium carbonate solution or 5 % ammonium hydroxide solution to result in pH = 7. The gel was dried for 3 hours in air and for 12 hours at 80 °C in a drying cabinet (gel- variant).
In another variant, the active ingredient - sol- solution is dried using a rotation evaporator on a water bath (80 °C-). (sol-variant).
The resulting granulates are investigated by x-ray diffraction and the release properties of the Carbamacepin in a 1 % aqueous dodecyl sulfate solution are determined by spectroscopy in a suitable release equipment . A comparison is made to a commercial retard- preparation, as well as to the pure ingredient (see fig 1, 2).

Table 1.1
Processing for synthesis of different Carbamacepin - SiO_2 - composites
(in relation to 1 g of the active ingredient Carbamacepin)

No.	ml Sol A	Solvent	Active ingr.:SiO_2	Additive	Variant
C1	25	Ethanol	1:1	-	Gel
C2	50	Dioxan	1:2	-	Gel
C3	100	Ethylglykol	1:4	-	Gel
C4	100	"	1:4	1.0 g Sorbit	Gel
C5	100	"	1:4	3 ml PDMDAAC(40%)	Gel
C6	100	"	1:4	2 g Dibutylphthalat	Gel

Example 1.3 :

Nifedipin - SiO_2 - composites

Introduction of the active ingredient Nifedipin into the SiO_2 - matrix

The processing is the same as in example 1.1. The release kinetics of the granulates are determined in 50 % acetic acid in a suitable equipment. A comparison is made to a commercial retard- preparation, as well as to the pure ingredient (see fig 3 , 4).
The results correspond to the release data as obtained for water / ethanol (7 : 1) in a paddle agitator (DAB 10), as well as for 0.1 N -hydrochloric acid in a through flow cell type A (DAB 10).

Table 1.2
Processing for synthesis of different Nifedipin - SiO_2 - composites
(in relation to 1 g of the active ingredient Nifedipin)

No.	ml Sol A	Solvent	Active ingr./SiO_2	Additive	Variant
N1	125	Ethanol	1:5	-	Gel
N2	125	Ethylglykol	1:5	-	Gel
N3	125	Ethanol	1:5	-	Sol
N4	125	Ethylglykol	1:5	-	Sol
N5	250	Ethanol	1:10	-	Gel
N6	250	"	1:10	2g Saccharin-Na	Gel
N7	250	"	1:10	2g Na-Polystyren-sulfonat/Aldrich	Gel
N8	250	"	1:10	6 ml Aerosil-Dispersion K330 (Degussa)	Gel
N9	100	Ethylglykol	1:4	2g Dibutyl-phthalat	Gel

Example 1,4 :

Diclofenac - SiO_2 - composites

1 g Diclofenac and 0.2 g ammonium sulfate are dissolved under heating in 125 ml SiO_2 - sol (in water / ethylglycol) . After few minutes gelling takes place. The gel is dried in air for 3 h and for 12 h at 80 °C. The release kinetics are determined in 1 % aqueous dodecyl sulfate solution (see fig. 5)

Example 1.5 :

Active bases - SiO_2 - composites

(a) 1 g of the liquid ingredient base Clomipramin or 1 g of low melting Trimipramin are dissolved in 62.5 ml SiO_2 - sol (in water / ethyl glycol) and 0,2 g glycerin monohexyl ether Gellation is obtained after a short time heating. The gel is dried for 3 hours in air and for 12 hours at 50 °C in a drying cabinet The release kinetics of the active ingredients were determined in 0.1 n hydrochloric acid (see fig. 6) and compared to the release of pure Trimipramine (curve C1. T1 in Fig . 6)
(b) 0.24 g Clomipromin and 0.24 g dibutyl phthalate are under slight heating dissolved in 20 ml sol B The clear solution gelles solidly over night. The gel is dried for 3 hours in air and for 12 hours at 60 °C in a drying cabinet . (Release curve C2 in fig. 6)
(c) 0.3 g Trimipramine is dissolved in 50 ml sol C and added to an aqueous 10 % solution of polyacrylic acid 10 000 (Na-salt, Fluka). Further processing as in (b) . The release curve T2 is seen in fig. 6.

Example 1.6 :

Vitamin K3- composites

(a) 0.24 g vitamin K3 (Menadon, Merck) and 0.24 g dibutyl phthalate are dissolved in sol B using slight heating. The clear solution gels over night. The gel is dried for 3 hours in air and for 12 hours in a drying cabinet with exclusion of light . The release kinetics were determined in n-propanol / water (50 / 50) . (See curve V1 in fig. 7)
(b) 0.3 g vitamin K3 and 0.24 g paraffin oil are dissolved in 5 ml methyl glycol and then mixed with 50 ml sol C. Further processing is according to (a). The release curve V2 for the active ingredient - composite can be seen in fig. 7 .

Invention Example 2

For the manufacture of powders or film layers one dissolves a liquid to be incorporated into an organic - water -metal oxide- sol, which can be synthesized by known processes by acid or alkaline hydrolysis of metal alkoxides (preferred silicon-, aluminum-, or titanium alkoxides or their mixtures) in an organic solvent compatibly with water see C. J. Brinker, G. W Scherer: Sol- Gel -Science, Acad. Press, Inc, San Diego, 1990.
In special cases one can also use sols consisting of metal oxides and alkylated metal oxides (and which e. g. can be formed by simultaneous hydrolysis of tetraalkoxy silanes and trialkoxyalkyl silanes) . The liquids to be encapsulated can then be added before simultaneously or after the synthesis of the metal oxide sols. Requirements to the liquids are mainly . that they must be soluble in the sol, and that their boiling point is well above the solvent of the sol, preferred above 100 °C at normal pressure (10^5 Pa). The weight proportion liquid : metal oxide is preferred in the between 0.01 : 1 and 0.3 : 1 range; where these limits can be extended.
Restrictions with respect to structure of the liquids have not been found. Without problem one can use mixtures of liquids as well as liquids of natural origin (ethereal oils, plant extracts, animal secretions). Since the synthesis generally uses neutral pH and moderate temperatures (below 50 °C), one can use liquids which are sensitive to hydrolysis and temperature. The metal oxide sol water content as well as the type of organic solvent used with the water can be adjusted according to the solubility of the liquid to be encapsulated., e. g. it is of advantage for water insoluble liquids and oils to use low water content metal oxide sols and approtic solvents such as acetone, dioxane, dimethyl formamide or high boiling alcohols such as methoxy- propanol or ethyl glycol, so that the water can be removed together with the organic solvent.
The metal oxide- sols loaded with liquid or oil can then be converted to a solid by several processes:
(a) the sol can be directly converted to a metal oxide powder with the liquid encapsulated by careful drying . This method is of advantage, when low water content metal oxide sols are used and there is a considerable difference between the boiling points (more than 50 °C) of the sol-solvent and the liquid to be encapsulated..

(b) The sol loaded with the liquid to be encapsulated is converted to the gel by heating or by adjusting the pH (adjusting the basic or acid metal oxide sol to the neutral point). The solid gel contains the liquid to be encapsulated in homogeneous distribution. By removal of the solvent using standard drying processes, one obtains dry free flowing powders with the liquid incorporated.
(c) The metal oxide sol loaded with a liquid to be encapsulated can be coated and dried by standard processes (e. g. dipping, flow coating, spin coating) , possibly with addition of a wetting agent to improve adhesion to the carrier desired (e. g. polymer or metal foil, paper, textiles or wood). One obtains a transparent metal oxide film with the high boiling liquid incorporated.
Proof of the presence of encapsulated liquid in the metal oxide powders and film can be obtained by thermal or extracted release from the metal oxide matrix followed by spectroscopy. see examples.
As these investigations showed, the liquid is stably included in the metal oxide matrix. The evaporation rate from matrixes according to the invention processes is much less, than is found for liquids adsorbed in porous metal oxide layers, see fig 8.
For many applications it is necessary. to release the liquid at controlled rate from the metal oxide matrix. This can be achieved through thermal or extraction means. While the release of the encapsulated liquid is very low at room temperature, the release rate increases with increasing temperature in dependence upon the vapor pressure of the liquid. see fig. 9. This way one can control the release of the liquid to the surrounding gas phase. The release of liquid from the metal oxide matrix to a surrounding liquid phase can, in addition to depending upon selection of the metal oxide sol (see fig. 11). also be especially controlled by addition of penetrating compounds, which can be added to the metal oxide sol in weight proportions up to 100 % related to the metal oxide, at processing before, during or after the synthesis of the sol. The penetration compounds increase the rate of release of included liquid from the metal matrix as seen in Fig. 12. This is due to increase in the permeability due to out- dissolving or to swelling. Especially useful penetration compounds were found to be low molecular water soluble materials, such as sacharide -derivatives, salts or amides of organic acid or ammonium salts of water soluble polyanionic compounds such as polystyrenesulfonic acid, polyacrylic acid or carboxymethyl cellulose or poly -cationic compounds such as polydimethyldiallyl ammonium chloride.
It is also possible to add a second liquid, so that depending upon the solubility of the liquid active ingredient in the added liquid and upon the surrounding solvent phase one can achieve retardation or acceleration of the release Fig. 13 shows the case, where the addition of a high boiling liquid such as dibutyl phthalate or paraffin oil does retard the release of the oil type liquid vitamin E.
The invention process is advantageous by using simple technology to encapsulate practically any organic liquid and oil with a boiling point well above the boiling point of the liquid phase of the sol. The powders and films manufactured according to the invention are solid materials where the organic liquids and oils are incorporated, resulting in long- term stability at room temperature. The release of the incorporated liquids and oils can be controlled by heating or by addition of penetrating aids.

Application of the metal oxide powders and films with incorporated organic liquids and oils were e. g.
- solids or thin layers with aimed release for use in pharmacy using liquid or oil type active ingredients and vitamins on synthetic or natural basis. Specific application for solids or thin layers with aimed release are transdermal systems with liquid or oily active ingredients (e. g. nitroglycerin) . By addition of specific penetration aids (ureic acid. oils such as glycerin ether) the transport of the active ingredient through the skin can be assisted
- solids or thin layers with aimed release for use in cosmetics and body care products by use of liquid or oily scents and skin care agents on synthetic or natural basis.
- solids or thin layers with aimed release for use as disinfectants (e. g. for pest control. plant protection) by use of liquid or oily pheromones. bacteriocides or pesticides on synthetic or natural basis
- of encapsulated scents and attractants.
From the magnitude of product variations some examples are further described in the following.

Example 2.1 :

Synthesis of metal oxide sols

(A) SiO_2 - sol

50 ml tetraethoxy silane, 200 ml ethanol (ethyl glycol, dioxane) and 100 ml 0.01 N hydrochloric acid (or 5 % ammonium hydroxide) are stirred for 20 hours at room temperature.

(B) Sol from SiO_2 / MeSi O x

35 ml tetraethoxy silane, 15 ml tetraethoxy-methyl silane is dissolved in 200 ml ethanol and 100 ml 0.01 N hydrochloric acid and stirred for 20 hours at room temperature.

(C) Sol from SiO_2 / TiO_2

To 45 ml tetraethoxy silane. 5 ml tetraisopropyl ortho-titanate in 200 ml ethanol is slowly dripped 10 ml 0 1 N hydrochloric acid and stirred for 20 hours.

(D) Sol from SiO_2 / Al_2O_3

Into 45 ml tetraethoxy silane and 200 ml ethanol is dissolved under heating 5 g aluminum triisopropylate. Then at room temperature under agitation, is slowly dripped in 10 ml 0.1 N hydrochloric acid. The clear solution starts to gel slowly after about 3 hours. It is then immediately further processed.

Example 2.2:

Encapsulation of the scents Limonen, Ionon, Famesol, as well as the Hochsieder dibutyl phthalate and paraffin oil.

I g of the respective liquid is dissolved in 50 ml acid hydrolyzed SiO_2- sol A (in water / ethyl glycol), and gelled under slight heating and with dripping in of 5 % ammonium hydroxide. The solidified gel is then dried for 20 hours in air, resulting in a light glassy powder.
A comparison of the release from the invention incorporated Limonen, with the release of 1 g Limonen, adsorbed on 5 g diatomaceous earth / Fluka, or on Al_2O_3 - powder / Labor Chemie Apolda is seen in Fig. 8.
The release of the invention incorporated alpha- Ionon from the SiO_2- matrix at 20, 50, and 80 °C within 130 min. is shown in fig. 9. The release of the above listed organic liquids and oils with heating to 50 °C can be seen in fig. 10.

Example 2.3 :

Metal oxide - films with the incorporated liquid active ingredient - base Clomipramin.

One prepares a base -solution of 1 g Clomipramin and 10 ml ethyl glycol (" base - solution"). 10 ml metal oxide sol and 1 ml base -solution are dissolved , possibly with addition of a control material, and the clear solution is coated over a film base (140 µm acetyl cellulose). After drying in air one obtains clear films.
The release of the Clomipramin from the metal oxide matrix was determined as follows:

1 x 3 cm^2 of the coated film was treated with 3 ml phosphate buffer, pH 6.8, in a cuvette and the concentration of the released active ingredient Clomipramin over time was determined by spectrometry (max. at 285 nm).

Table 2.1 : Recipes

(a) Different metal oxide sols (see fig 11)

SiO_2 / EtOH	1 ml base-solution + 10 ml sol A in ethanol
SiO_2 / EtGl	1 ml base-solution + 10 ml sol A in ethylene glycol
SiO_2 / MeSi O Me_3	1 ml base-solution + 10 ml sol B
SiO_2 / TiO_2	1 ml base-solution + 10 ml sol C
SiO_2 / Al_2O_3	1 ml base-solution + 10 ml sol D

(b) Addition of different penetration materials (see Fig. 12)

SiO_2	1 ml base-solution + 10 ml sol A in ethanol	
Ureic acid	as above	+ 0.1 g ureic acid
PAA :		+ 1 ml 5% poly-acrylate 20000 / Fluka
PSS :		+ 2 ml 2 % Na-styrene sulfonate 70000 / Aldrich
Sorbitol		= 1 ml 10 % sorbitol
Ammonsulfat:		= 1 ml 10 % ammonium sulfate

Example 2.4 :

Metal oxide coatings with incorporated vitamin E (Tocopherol)

One prepare a base -solution of 1 g of vitamin E oil and 10 ml ethylene glycol. ("Base-solution"). 10 ml metal oxide sol and 1 ml base -solution are dissolved , possibly with addition of a control material. and the clear solution is coated over glossy cardboard. After drying in air one obtains well adhering coatings.
The release of the vitamin E from the metal oxide matrix was determined as follows:
1 x 3 cm^2 of the coated cardboard was treated with 3 ml 30 % n- propanol in water in a cuvette and the concentration of the released vitamin E over time was determined by spectrometry (Max at 292 nm) , see fig. 13.

Table 2.2

Recipes

SiO_2 :	1 ml base-solution + 1 ml sol A in 90 % ethanol
PDMDAAC :	as above + 1 ml 4 % polydimethyldiallyl ammonium chloride in water
Na - ascorbate	+ 1 ml 10 % sodium ascorbate in water
PDPh	+ 0.1 g dibutyl phthalate
paraffin oil	+ 0.1 g paraffin oil AB

The release is seen in fig. 13.

Patent Claims

1. A composite consisting of a solid matrix material and at least one component incorporated into the matrix, where the matrix material is formed by a metal oxide matrix, **recognized by the feature, that**
the component is homogeneously and molecularly dispers incorporated into the matrix.

2. A composite according to claim 1, where the incorporated component consists of an active ingredient, which can be released, and the matrix material consists of SiO_2, which can be partly replaced by Al_2O_3 or MgO, where the composite is formed as a voluminous material, especially shaped as particles, granulates or tablets.

3 A composite according to claims 1 or 2, **recognized by the feature, that** the weight proportion of the active ingredient : matrix is in the region 0.05 : 1 to 1 : 1.

4. A composite according to claims 1 to 3, **recognized by the feature, that** there further is incorporated at least one control material into the metal oxide matrix.

5. A composite according to claim 4, **recognized by the feature, that** the weight proportion of the control material : matrix is in the region 0.05 : 1 to 1 : 1.

6. A composite according to claims 4 or 5, **recognized by the feature, that** one as control material, introduces:

- low molecular, water soluble materials such as sacharide derivatives, salts or amides of organic acids or ammonium salts
- water soluble polyionic compounds such as Na-polystyrene sulfonate, salts of

the polyacrylic acid. carboxymethyl cellulose, dextrane sulfate or polycationic compounds such as polydimethyl diallyl ammonium chloride,
-micro-porous fillers such as solid or dispersed aerosils or
-high boiling liquids such as phthalic acid ester, glycine ether or paraffin oil.

7. A composite according to one of the previous claims , **recognized by the feature, that** at least one active ingredient is formed as a liquid or solid material of plant or organic origin and which has biologic activity in living organisms.

8. A composite according to one of the previous claims , **recognized by the feature, that** at the incorporated active ingredient is a pharmaceutical active ingredient, especially one of the active ingredients Alprazolam, Carbamazepin, Clomipramin, Clodin, Detajmiumbitartrate, Diclofenac, Dazepam, Glibenclamid, Medazepam, Metoclopramid, Nifedipin, Pentoxifyllin, Prazosin, Talinolol, Trimipramin, Verapamil or Vitamin K3 .

9. A composite according to claim 1 , whereby are formed metal oxide powders or films which at least contain one incorporated organic liquid and / or an oil.

10. . A composite according to claim 9 , where the metal oxide is SiO_2, Al_2O_3, TiO_2 or a mixture thereof.

11. . A composite according to claims 9 or 10 , where the organic liquids and / or oils boil at a temperature above 100°C (at normal pressure of 10^6 Pa).

12. . A composite according to claim 9 to 11 , where the the weight proportion of the liquid : matrix is in the region 0.01 : 1 to 0. 3 : 1.

13. . A composite according to claim 9 to 11 , where there is included one or more penetration materials, where the part of the penetration material(s) is up to 100 w. % in relating to the metal oxide.

14. A composite according to claim 13, where the penetration material is:
- a low molecular, water soluble materials such as sacharide derivatives, salts or amides of organic acids or ammonium salts or
- water soluble polyionic compounds such as polystyrenesulfonic acid, polyacrylic acid, carboxymethyl cellulose or polycationic compounds such as polydimethyldiallyl ammonium chloride.

15. A composite according to claim 9 to 14, where the organic liquid and / or the oil incorporated is mixed with a second higher boiling liquid.

16 . A process for manufacture of composites consisting of a metal oxide matrix and of at least one active ingredient which can be released,
recognized by the steps:
(a) manufacture of a metal oxide sol dissolved in an organic solvent which can be mixed with water and which contains SiO_2. SiO_2 / Al_2O_3 or SiO_2 / MgO,
(b) dissolution of an active ingredient in the metal oxide sol, and
(c) gellation by temperature increase or by pH- adjustment and /. or by removal of the solvent to form
a volunenous composite material.

17 . A process according to claim 16, **recognized by the feature, that** the metal oxide sol is synthesized by hydrolysis of a tertraalkoxy silane. to which for modification parts of metal alkoxides can be added.

18 . A process according to claim 16 or 17, **recognized by the feature, that** there to the solution of the active ingredient and metal oxide sol at least is added one control material. which does modify the active material release.

19 . A process for manufacture of composites according to one or more of the claims from 9 to 15, where the organic liquid or an oil, possibly in the presence of a penetration material or in the mixture of two high boiling liquids. is dissolved in the aqueous metal oxide sol and where the solvent then either is removed directly from the sol or is removed after the subsequent gellation from the gel.

20. A process for manufacture of composites according to one or more of the claims from 9 to 15, where the organic liquid or an oil, possibly in the presence of a penetration material or in the mixture of two high boiling liquids. is dissolved in the aqueous metal oxide sol, and then is coated from solution onto a carrier.

21. Use of the composite according to claims 1 to 8 for manufacture of pharmaceuticals, such as powders , dragees, tablets, film tablets, capsules, suspensions. half solid forms, or for manufacture of pharmaceuticals, which contain especially Alprazolam, Carbamazepin, Clomipramin, Clodin, Detajmiumbitartrate, Diclofenac, Dazepam, Glibenclamid, Medazepam, Metoclopramid, Nifedipin, Pentoxifyllin, Prazosin, Talinolol, Trimipramin, Verapamil, or Vitamin K_3 .

22. Use of the composite according to claims 9 to 15 for manufacture of pharmaceuticals, cosmetics, body care products, bacteriostatics or bacteriocidins, insecticides and pesticides and / for manufacture of transdermal systems.

Carbamazepin - Release
(from granulates, in relation to 200 mg Carbam.)

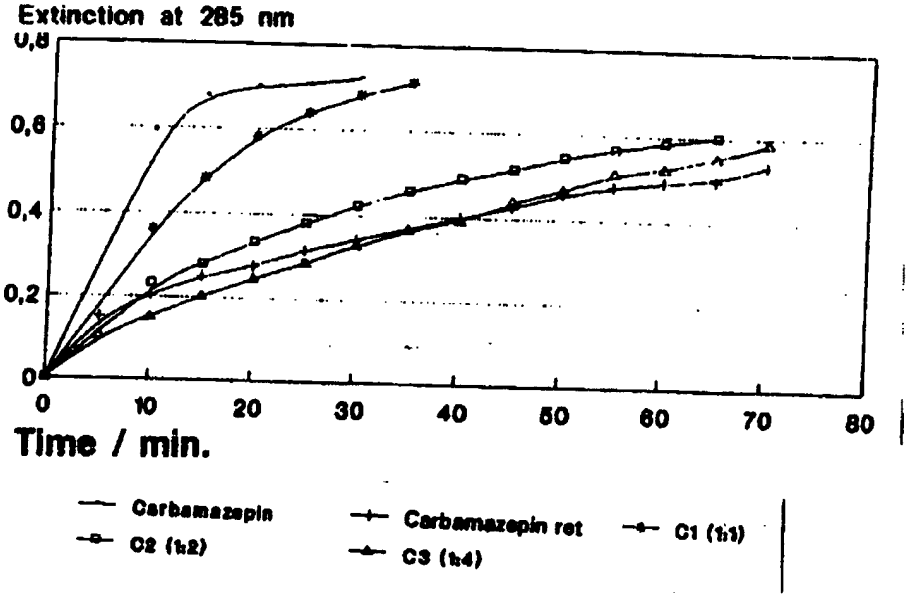


Fig 1 : Influence of the active ingredient : SiO2 ratio

Carbamazepin - Release
(from granulates, in relation to 200 mg Carbam.)

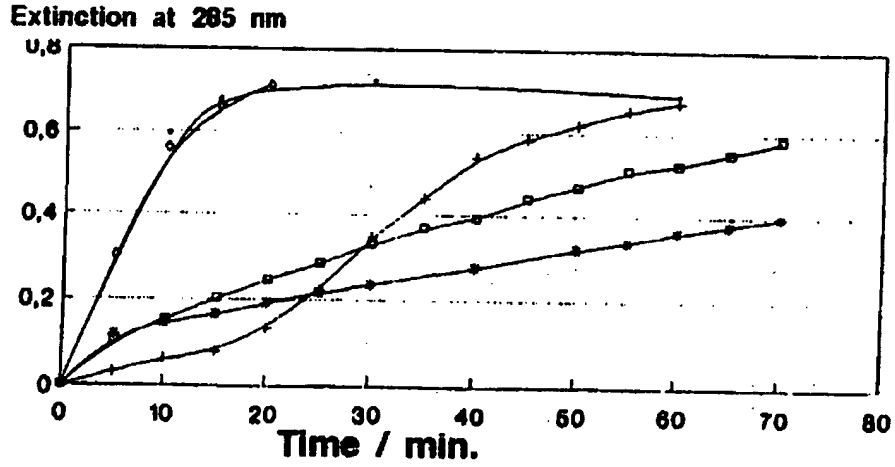


Fig 2 : Influence of additives.

Nifedipin - Release
(from granulates, in relation to 40 mg Nif.)

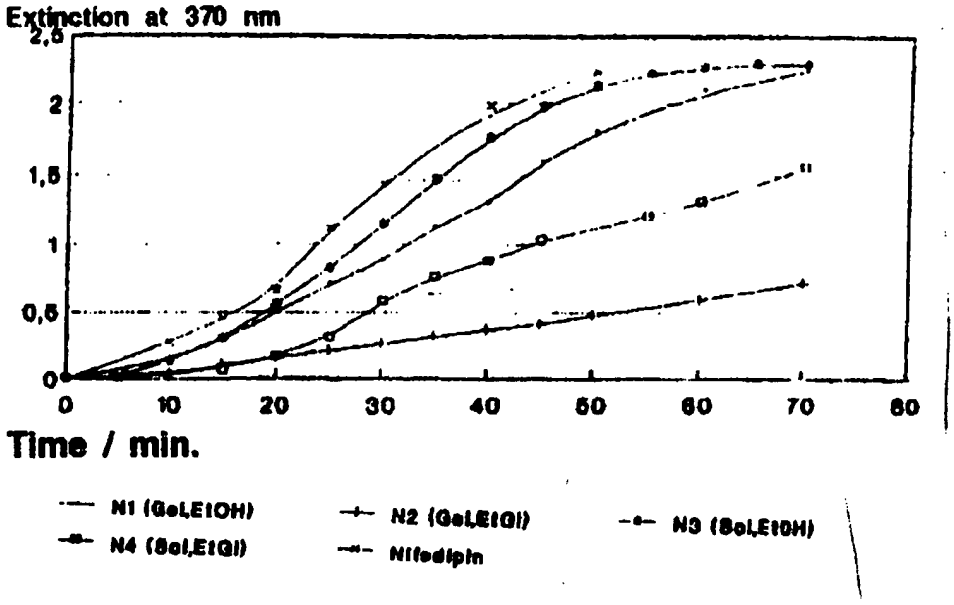


Fig 3 : Influence of different sol - gel variants

Nifedipinpin - Release
(from granulates, in relation to 40 mg Nif.)

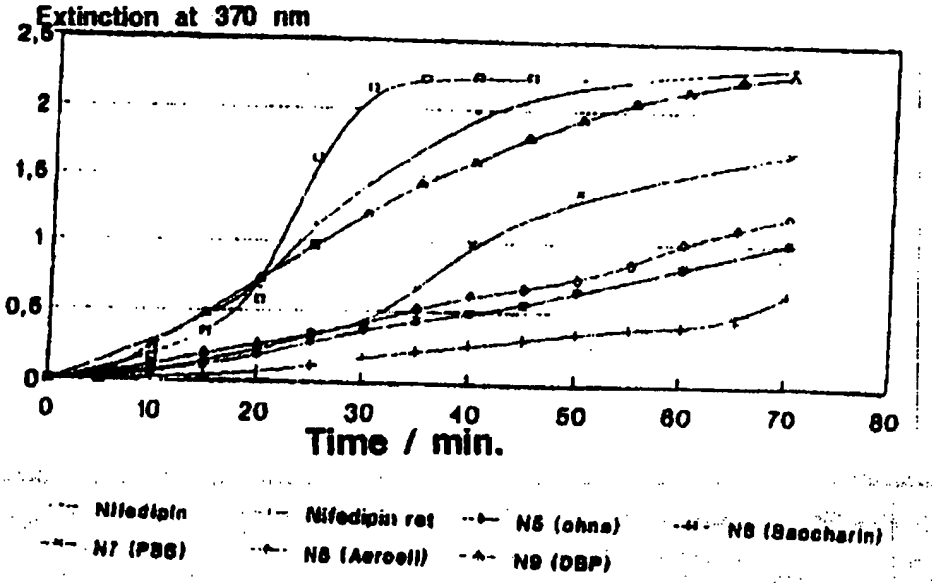


Fig 4 : Influence of additives.

Diclofenac - Release
(proportion of active ingredient to 50 mg)

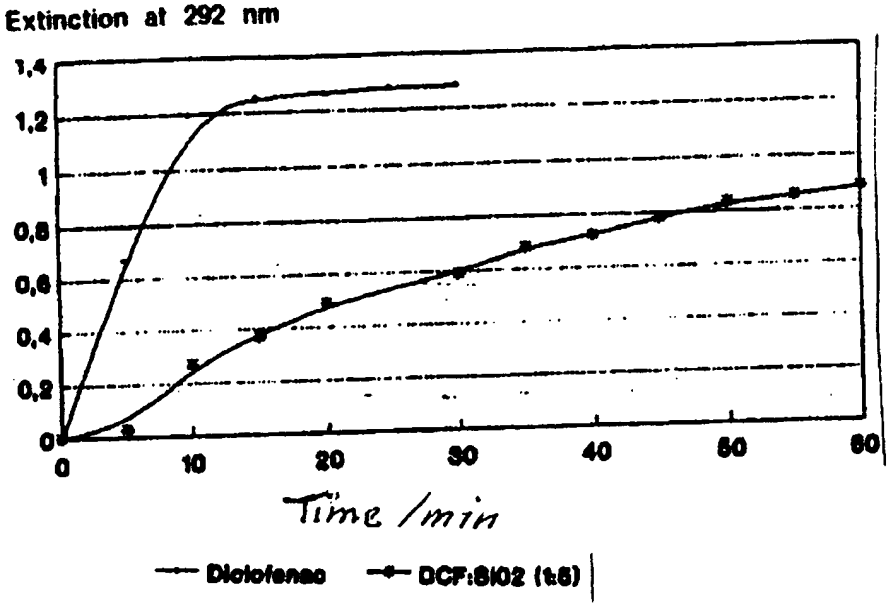


Fig 5 : Influence of the SiO2 -encapsulation

Release of active ingredient bases
(proportion of active ingredient to 30 mg)

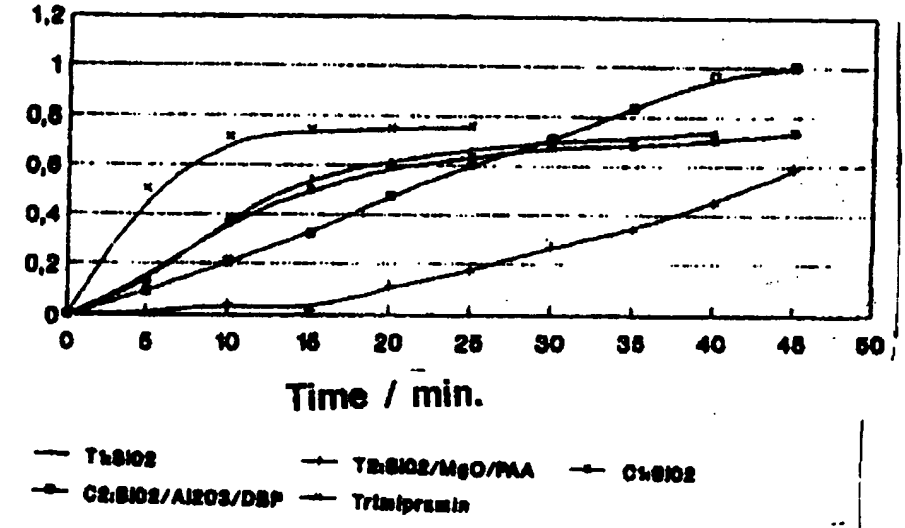


Fig 6 : Metal oxide encapsulation of clomipramin (Cl) and Trimipramin (T)

Vitamin K3 - Release
(Granulate in based upon 40 mg K3)

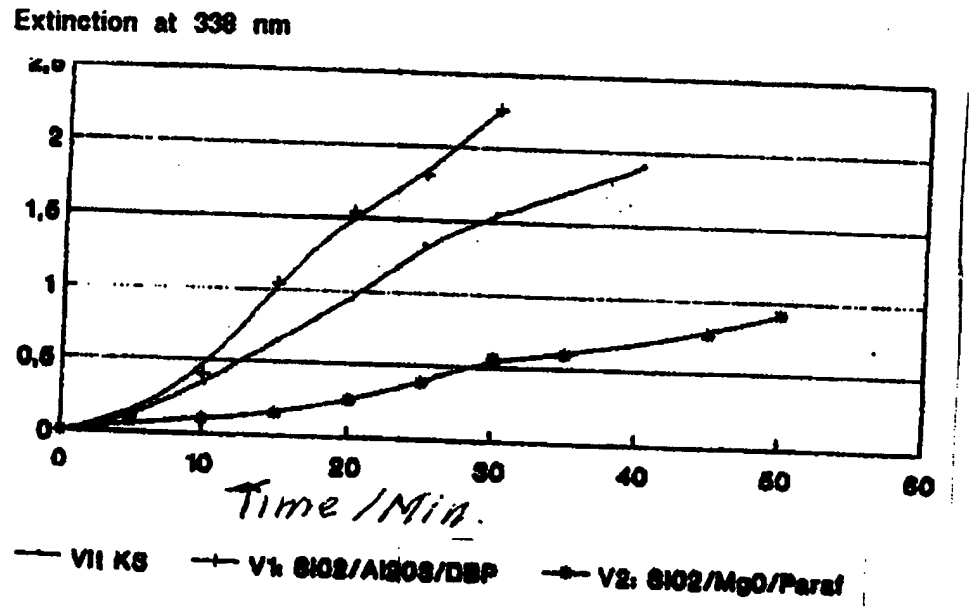


Fig 7 :Release of vitamin K3 in 50 % propanol

Fig.8: Limonen - Release (50 °C)

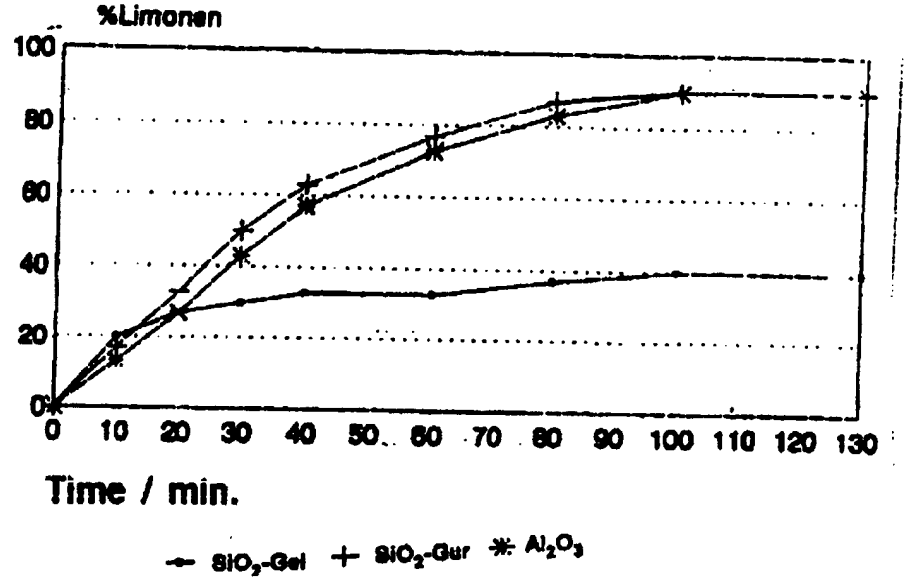


Fig 9: Release of alpha Ionon

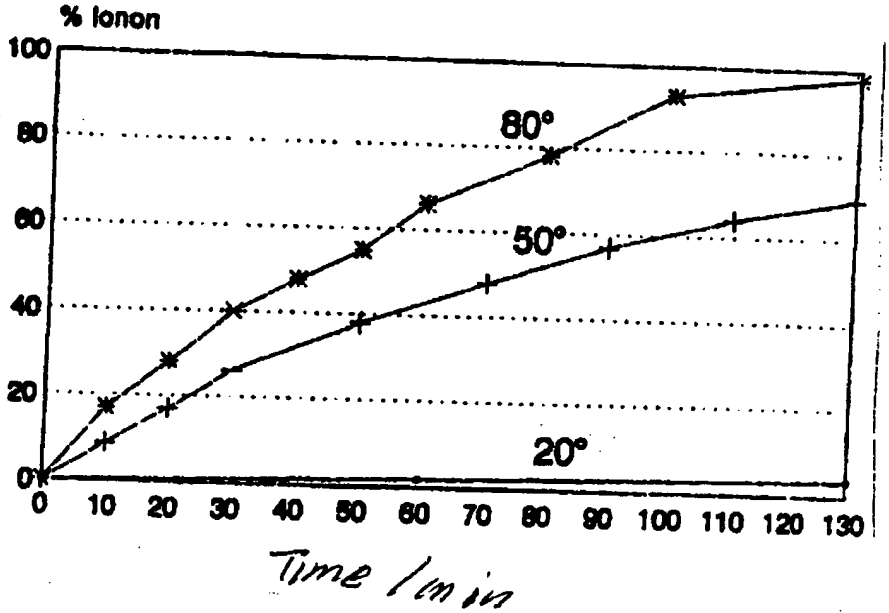


Fig 6 : Metal oxide encapsulation of clomipramin (Cl) and Trimipramin (T)

Fig. 10 Thermal release from SiO_2 - gels (50°C)

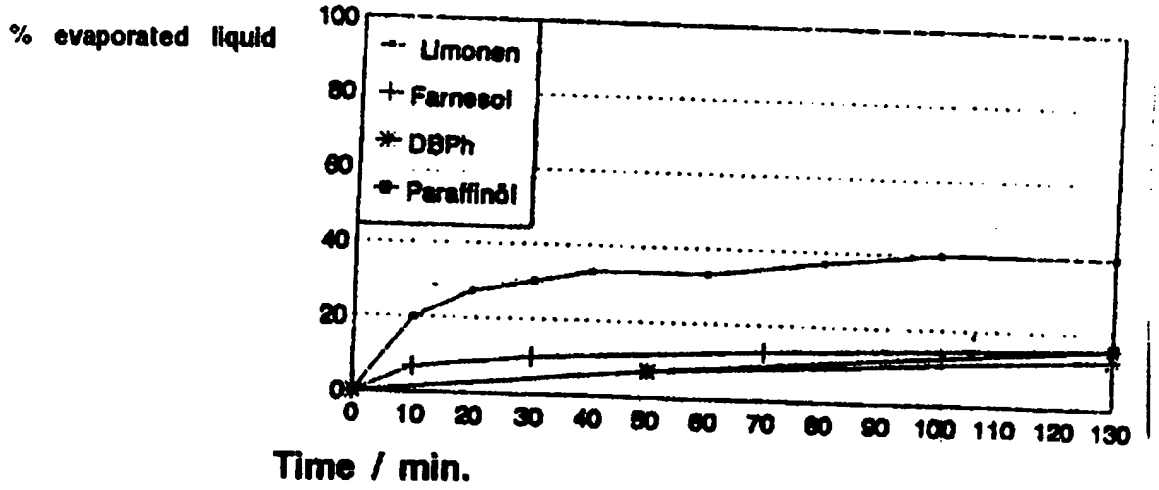
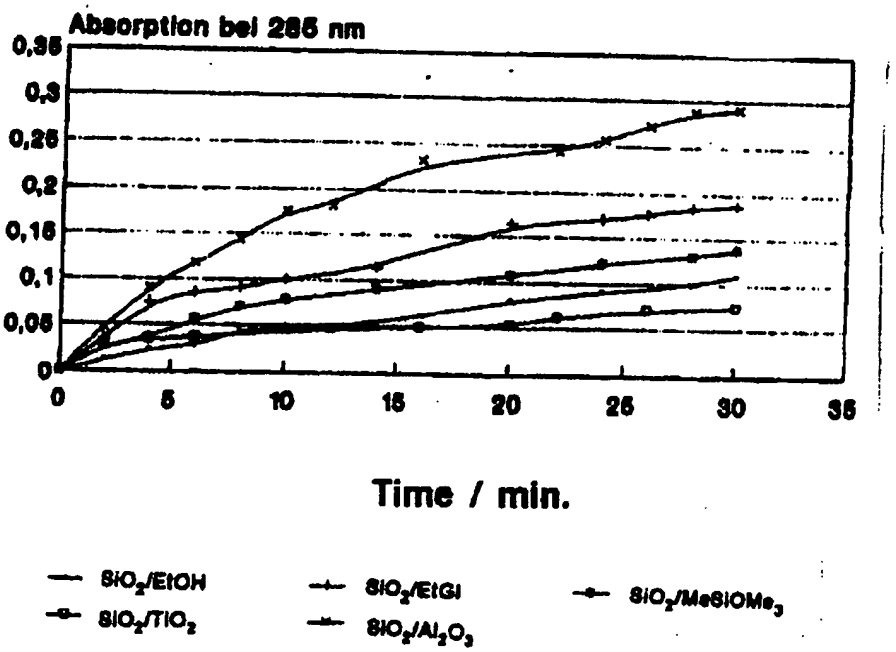


Fig. 11 : Active ingredient release from Clomipramin films with various Metal oxides



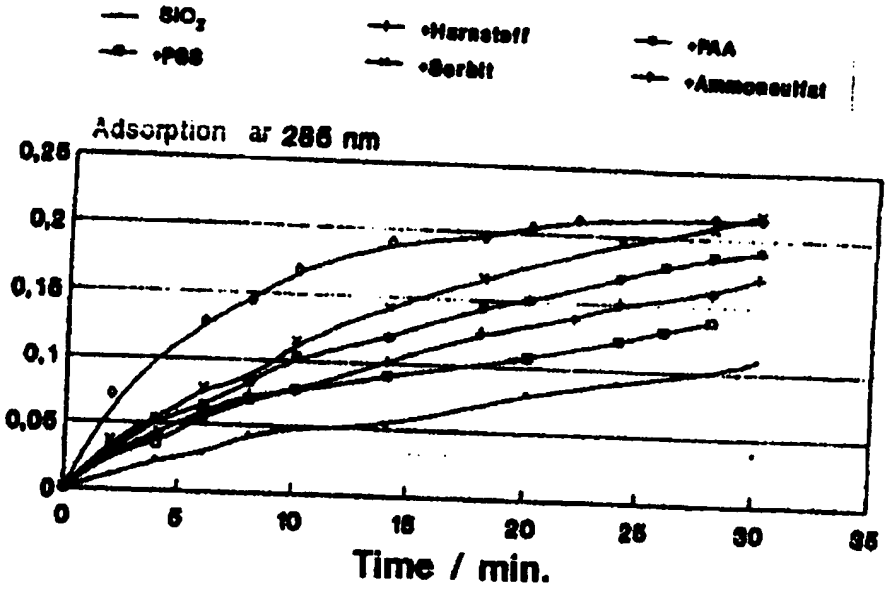


Fig. 12 : Active ingredient release from Clomipramin films with various penetration materials

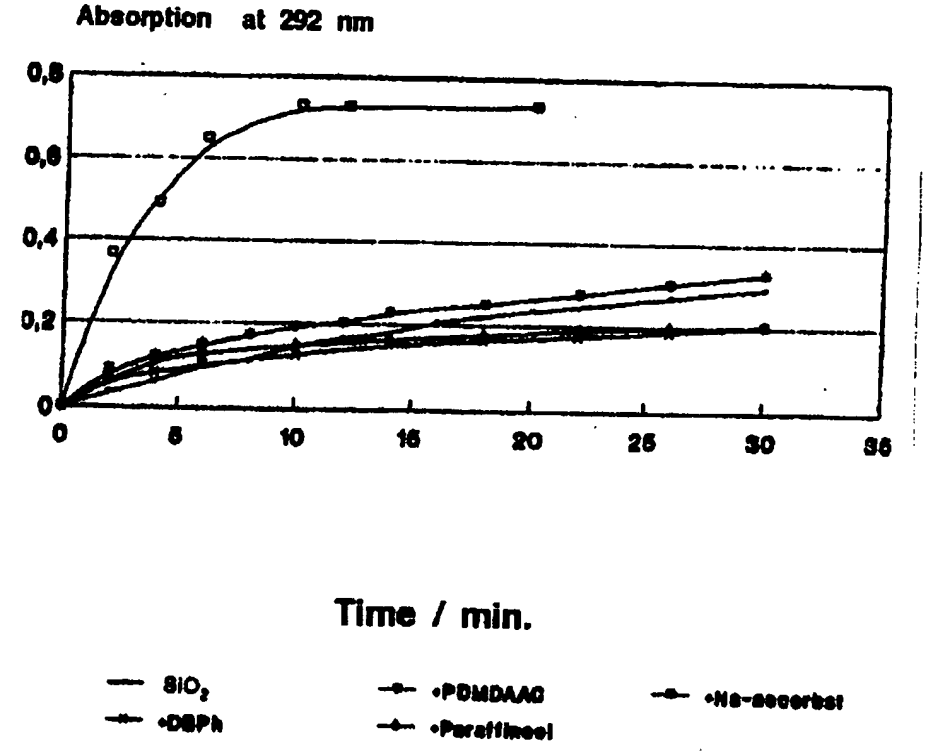


Fig. 13: Active ingredient release from vitamin E films with various penetration materials or a second added liquid.

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54 Metal oxide composite with regulated release of active ingredients.

57 The invention concerns composites of a metal oxide matrix and at least and one incorporated homogeneous, molecularly disperse and non crystalline component. A process for its manufacture. as well as applications for the composites.
The incorporated component can include an active ingredient and possibly one or more control materials.
As active ingredients one can use liquid or solid materials of plant or organic origin, which interact biologically with living organism.

The active ingredients are introduced into the silicon dioxide matrix by sol-gel technology.
As control materials one can use low-molecular water-soluble materials, polyionic compounds, microporous fillers as well as high-boiling solvents.
The release of organic liquids or oils from the matrix can be controlled either by penetrating materials or by controlled temperature increase.
The composites according to the invention find use in the production of pharmaceuticals, cosmetics, body care products, bacteriostatics or bacteriocidins, insecticides and pesticides.